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(19)(CA) **CANADIAN PATENT** (12)

(54) Preparation of O-Substituted Hydroxylamine Hydrochlorides

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NO DRAWING

Preparation of O-substituted hydroxylamine hydrochlorides

The present invention relates to a novel process for the preparation of O-substituted hydroxylamine hydrochlorides of the formula I

$$R\text{-}O\text{-}NH_2 \cdot HCl \qquad (I)$$

where R is C_1-C_4-alkyl, C_3- or C_4-alkenyl, C_3- or C_4-haloalkenyl or benzyl.

A large number of methods are known for the preparation of O-substituted hydroxylamines, but the methods are technically and economically unsatisfactory.

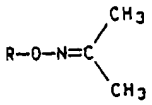
In particular, Houben-Weyl, Methoden der organischen Chemie, Volume 10/1, 4th Edition, 1971, 1186-1189, discloses that certain aldoxime and ketoxime ethers can be hydrolyzed with mineral acids to give the corresponding salts of O-substituted hydroxylamine; however, the yields obtainable are unsatisfactory.

It is an object of the present invention to make the O-substituted hydroxylamines I which are important for the synthesis of drugs and crop protection agents more readily available technically and economically.

We have found that this object is achieved by a process for the preparation of O-substituted hydroxylamine hydrochlorides of the general formula I

$$R\text{-}O\text{-}NH_2 \cdot HCl \qquad (I)$$

where R is C_1-C_4-alkyl, C_3- or C_4-alkenyl, C_3- or C_4-haloalkenyl or benzyl, by cleaving the corresponding acetoxime ether of the general formula II



(II),

wherein, according to the invention, the cleavage is carried out continuously in a reaction column containing not less than 20 theoretical plates with constant removal of the acetone eliminated, using hydrogen chloride and water.

R is, for example,

- C_1-C_4-alkyl, ie. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl and tert-butyl,
- C_3- or C_4-alkenyl, such as prop-2-enyl, but-2-enyl and but-3-enyl,
- C_3- or C_4-haloalkenyl, such as 3-chloroprop-2-enyl, 2-chloroprop-2-enyl, 2-chlorobut-2-enyl, 3-chlorobut-2-enyl, 2,3-dichloroprop-2-enyl, 2,3-dichlorobut-2-enyl, 3-bromoprop-2-enyl, 3-fluoroprop-2-enyl, 2-bromoprop-2-enyl, 2-fluoroprop-2-enyl, 2,3-dibromoprop-2-enyl and 2,3-dibromobut-2-enyl, or
- benzyl.

The starting compounds II are known or are obtainable by known methods, for example by etherification of acetoxime (German Laid-Open Applications DOS 2,927,117, EP-A-121 701 and EP-A-158 159).

Regarding the conversion of the acetoxime ethers II to the O-substituted hydroxylamine hydrochlorides I, the following may be stated:

Particularly suitable reaction columns are tray columns of any design, especially bubble cap columns, since the residence times on the trays can be readily adjusted in these columns. Packed columns are also suitable. The number of theoretical plates is generally from 20 to 60, preferably from 30 to 50, although the upper limit for the number of plates is determined only by economic considerations.

The hydrogen chloride required for the hydrolysis is preferably used in a stoichiometric amount, although it is also possible to use an excess, for example up to 1 mole per mole of acetoxime ether II.

Where aqueous hydrochloric acid is used, its concentration is preferably from 10 to 20, in particular from 15 to 20, % by weight.

In a preferred embodiment, the procedure can be carried out in the presence of 1,4-dioxane, from which the hydroxylamine I can readily be obtained in crystalline

form. In this case, however, the amount of water used must be as small as possible (i.e. 1 to 1.6 mole water for 1 mole acetoxime ether II) and furthermore hydrogen chloride must therefore be used in gaseous form.

Otherwise, the reactant II, a solution of II, water and hydrogen chloride or aqueous hydrochloric acid are advantageously fed in at the middle of the column, and the feed rate and heating power are chosen so that the mean residence time in the column is from 3 to 4 hours. The general rule with regard to the feed point is that compounds II having a higher boiling point are introduced at a higher tray than those having a low boiling point. The reaction temperature is advantageously from 70 to 140°C, so that the procedure can be carried out under atmospheric pressure; if necessary, slightly reduced pressure down to about 500 mbar or slightly superatmospheric pressure up to about 3 bar may be used. The acetone taken off continuously at the top at a reflux ratio of, for example, from 1:5 to 1:50, preferably from 1:5 to 1:20, can be reused for the preparation of acetoxime ether II.

At the bottom of the column, an aqueous solution of O-substituted hydroxylamine hydrochloride I or a suspension of I in 1,4-dioxane is obtained.

This solution or suspension is discharged continuously and, if necessary, is worked up to give the pure products I in a conventional manner by crystallization or by stripping off the liquid.

This gives the compounds I in a purity and in a yield high enough to permit them to be used directly for syntheses.

The O-substituted hydroxylamine hydrochlorides are useful intermediates for the preparation of drugs and crop protection agents.

Preparation of the O-substituted hydroxylamine hydrochlorides I

EXAMPLE 1

131.2 g of acetoxime ethyl ether in 237.5 g of

B

1,4-dioxane, 31.3 g of water and 47.3 g of hydrogen chloride were metered in, per hour, at the 30th tray of a bubble cap column which contained 60 trays, had an internal diameter of 50 mm and was equipped with a thin film evaporator and an automatic reflux divider. Acetone was taken off at the top at a reflux ratio of 1:15, and the dioxane/product mixture was removed as a bottom product. The latter was filtered off under suction and the solid dried under reduced pressure. 123.0 g/h (97% yield) of ethoxyamine hydrochloride (Compound 1) of melting point 133°C were obtained.

EXAMPLE 2

In the apparatus described above, 139.9 g/h of acetoxime trans-crotyl ether and 315 g/h of 1,4-dioxane were metered in at the 50th tray, 40.1 g/h of hydrogen chloride were metered in at the 20th tray and 25.8 g/h of water were metered in at the 30th tray. Acetone was taken off at the top at a reflux ratio of 1:16. After cooling, the product was filtered off under suction and dried under reduced pressure.

126.4 g/h (93% yield) of trans-crotyloxyamine hydrochloride (Compound 2) of melting point 169°C were obtained.

The O-substituted hydroxylamine hydrochlorides listed in Table 1 were obtained from the corresponding acetoximes II, similarly to Examples 1 and 2:

TABLE 1

$H_2N-O-R \cdot HCl$ (I)

Compound	R	mp. [°C]	Yield %
3	CH_3	150	96
4	$(CH_2)_2CH_3$	154	95
5	$(CH_2)_3CH_3$	153	93
6	$CH_2CH(CH_3)_2$	129	92
7	$(CH_2)_4CH_3$	149	91
8	$CH_2CH=CH_2$	168	94
9	trans-CH_2-CH=CHCl	180	92
10	$CH_2C(CH_3)=CH_2$	165	91
11	$CH_2C_6H_5$	225	91

EXAMPLE 3

In the bubble cap column described in Example 1, 113.3 g/h of acetoxime methyl ether were metered in at the 10th tray and 262.8 g/h of 18% strength aqueous hydrochloric acid were metered in at the 40th tray. Acetone was taken off at the top at a reflux ratio of 1:8, and the aqueous solution of the product was removed as a bottom product. 300.9 g/h of a 35% strength solution of methoxyamine hydrochloride (Compound 3) (≙105.3 g/h of dry substance, 97% yield) were obtained.

The O-substituted hydroxylamines I listed in Table 2 were obtained in the form of their hydrochlorides in aqueous solution, from the corresponding acetoxime ethers II, similarly to Example 3:

TABLE 2

$[H_2N-O-R \cdot HCl]_{aq}$ (I)

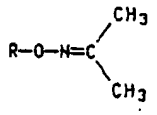
Compound	R	Yield %
1	CH_2CH_3	97
4	$CH_2CH_2CH_3$	95
8	$CH_2CH=CH_2$	93

We claim:-

1. A process for the preparation of an O-substituted hydroxylamine hydrochloride of the formula I

$$R\text{-}O\text{-}NH_2 \cdot HCl \qquad (I)$$

where R is C_1-C_4-alkyl, C_3- or C_4-alkenyl, C_3- or C_4-haloalkenyl or benzyl, by cleaving a corresponding acetoxime ether of the formula II



(II),

wherein the cleavage is carried out continuously in a reaction column containing not less than 20 theoretical plates with constant removal of the acetone eliminated, using hydrogen chloride and water.

2. A process as claimed in claim 1, wherein the cleavage is carried out using a stoichiometric amount of hydrogen chloride and acetoxime ether II.

3. A process as claimed in claim 1, wherein the hydrogen chloride is used in the form of 10-20% strength by weight hydrochloric acid.

4. A process as claimed in claim 1, wherein the hydrolysis is carried out in 1,4-dioxane as the solvent, with from 1 to 1.6 moles of water per mole of acetoxime ether II and while passing in hydrogen chloride gas.

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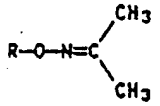
Abstract of the Disclosure: O-substituted hydroxylamine hydrochlorides I

$$R\text{-}O\text{-}NH_2 \cdot HCl \qquad (I)$$

where R is C_1-C_4-alkyl, C_3- or C_4-alkenyl, C_3- or C_4-haloalkenyl or benzyl, are prepared by continuous hydrolysis of the corresponding acetoxime ethers II



(II)

in a reaction column containing from 20 to 60 theoretical plates with constant removal of the acetone eliminated, using hydrogen chloride and water.